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Inventors: Sheu et al. Serial No.: 10/580,803

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This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A compound according to comprising formula (I) or (II)

wherein for both formula (I) and formula (II)

- R is (i) an amino acid or amino acid derivative group having antioxidant activity, or
 - (ii) a peptide comprising group, wherein said peptide group is two or more amino acids or amino acid derivatives, wherein the peptide and has antioxidant activity;

Z is a linker molecule containing 1 to about 20 atoms in a direct chain (i) $-Z^1-Z^2-$,

(ii)
$$-Z^{1}-O-Z^{2}-$$
,
(iii) $-Z^{1}-S-Z^{2}-$,
(iv) $-Z^{1}-N(H)-Z^{2}-$,
(v) $-Z^{1}-CO-N(H)-Z^{2}-$, or
(vi) $-Z^{1}-N(H)-CO-Z^{2}-$,

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- wherein Z¹ is an aliphatic or non-aliphatic Cl to C10

 hydrocarbon group; a single, fused or multi-ring

 aromatic group; or an aliphatic or non-aromatic

 cyclic group; and
- z² is an aliphatic or non-aliphatic C1 to C10 hydrocarbon group; a single, fused or multi-ring aromatic group; or an aliphatic or non-aromatic cyclic group; and
- Q^1 , Q^2 , and Q^3 are independently aliphatic Cl to C5 hydrocarbons hydrocarbon groups, or Q^2 and Q^3 together form an aliphatic N-heterocycle group;

wherein for formula (II), the N-heterocycle $\underline{\text{group}}$ possesses a quaternary nitrogen and Q^2 is optional.

Claim 2 (currently amended): The compound according to claim 1 wherein R is an amino acid or amino acid derivative group having antioxidant activity.

Claim 3 (currently amended): The compound according to claim 2 wherein the amino acid or amino acid derivative group is an L-amino acid or amino acid derivative.

Claim 4 (currently amended): The compound according to claim 2 wherein the amino acid or amino acid derivative group is an D-amino acid or amino acid derivative.

Claim 5 (currently amended): The compound according to claim 2 wherein \Re the amino acid or amino acid derivative group is selected from the group consisting of glutamic acid, cysteine, N-

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acetyl-cysteine, glycine, and 2,2-dialkylthiazolidine-4-carboxylic acid.

Claim 6 (currently amended): The compound according to claim 1 wherein R is a peptide group comprising from two up to ten amino acids or amino acid derivatives.

Claim 7 (currently amended): The compound according to claim 6 wherein R is a peptide comprising the peptide group comprises from two up to five amino acids or amino acid derivatives.

Claim 8 (currently amended): The compound according to claim 6 wherein the peptide group comprises at least one D-amino acid or amino acid derivative.

Claim 9 (currently amended): The compound according to claim 6 wherein the peptide group comprises only L-amino acids or amino acid derivatives.

Claim 10 (currently amended): The compound according to claim 6 wherein \Re the peptide group is selected from the group consisting of L- γ -glutamylcysteine, L- γ -glutamylglycine, L-cysteinylglycine, glutathione, L-carnosine, L-carnitine, and acetyl-L-carnitine.

Claim 11 (original): The compound according to claim 1 wherein the compound is selected from the group consisting of:

L-y-glutamyl-L-cysteinylglycine choline ester;

D-y-glutamyl-L-cysteinylglycine choline ester;

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L-cysteine choline ester;

L-γ-glutamyl-L-cysteine choline ester;

D-y-glutamyl-L-cysteine choline ester;

N-acetyl-L-cysteine choline ester;

D-2-(trimethylamino)ethyl-2,2-dimethylthiazolidine-4-carboxylic acid; and

L-2-(trimethylamino)ethyl-2,2-dimethylthiazolidine-4-carboxylic acid.

Claim 12 (original): The compound according to claim 1 wherein the compound is in the form of a pharmaceutically acceptable salt.

Claim 13 (canceled).

Claim 14 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is a direct link and \mathbf{Z}^2 is an aliphatic or non-aliphatic Cl to C10 hydrocarbon group.

Claim 15 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is a direct link and \mathbf{Z}^2 is a single, fused or multi-ring aromatic group.

Claim 16 (original): The compound according to claim 13 wherein \mathbf{Z}^1 is a direct link and \mathbf{Z}^2 is an aliphatic or non-aromatic cyclic group.

Claim 17 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is an aliphatic or non-aliphatic C1 to C10

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hydrocarbon group and \mathbf{Z}^2 is an aliphatic or non-aliphatic Cl to C10 hydrocarbon group.

Claim 18 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is an aliphatic or non-aliphatic Cl to C10 hydrocarbon group and \mathbf{Z}^2 is a single, fused or multi-ring aromatic group.

Claim 19 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is an aliphatic or non-aliphatic C1 to C10 hydrocarbon group and \mathbf{Z}^2 is an aliphatic or non-aromatic cyclic group.

Claim 20 (currently amended): The compound according to claim 13 wherein Z^1 is a single, fused or multi-ring aromatic group and Z^2 is an aliphatic or non-aliphatic C1 to C10 hydrocarbon group.

Claim 21 (currently amended): The compound according to claim 13 wherein Z^1 is a single, fused or multi-ring aromatic $\underline{\text{group}}$ and Z^2 is a single, fused or multi-ring aromatic $\underline{\text{group}}$.

Claim 22 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is a single, fused or multi-ring aromatic group and \mathbf{Z}^2 is an aliphatic or non-aromatic cyclic group.

Claim 23 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is an aliphatic or non-aromatic cyclic group

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and \mathbf{Z}^2 is an aliphatic or non-aliphatic Cl to C10 hydrocarbon group.

Claim 24 (currently amended): The compound according to claim 13 wherein \mathbf{Z}^1 is an aliphatic or non-aromatic cyclic group and \mathbf{Z}^2 is a single, fused or multi-ring aromatic group.

Claim 25 (original): The compound according to claim 13 wherein \mathbf{Z}^1 is an aliphatic or non-aromatic cyclic group and \mathbf{Z}^2 is an aliphatic or non-aliphatic cyclic group.

Claim 26 (original): The compound according to claim 1 having a structure according to formula (I).

Claim 27 (currently amended): The compound according to claim 26 wherein Q^1 , Q^2 , and Q^3 are independently aliphatic Cl to C5 hydrocarbons hydrocarbon group.

Claim 28 (currently amended): The compound according to claim 26 wherein Q^2 and Q^3 together form an aliphatic N-heterocycle group.

Claim 29 (original): The compound according to claim 1 having a structure according to formula (II).

Claim 30 (currently amended): The compound according to claim 29 wherein Q^2 is not present, <u>and</u> the N-heterocyclic amine comprising possessing a quaternary nitrogen selected from the

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group consisting of <u>is</u> pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, imidazolyl, or pyrazolyl, and pirazinyl.

Claim 31 (currently amended): The compound according to claim 29 wherein Q^2 is present, <u>and</u> the N-heterocyclic amine comprising possessing a quaternary nitrogen selected from the group consisting of is pyrrolyl, pyrrolidinyl, morpholinyl, and or piperidinyl.

Claim 32 (currently amended): A pharmaceutical composition comprising a pharmaceutically acceptable carrier and $\frac{1}{2}$ compound according to claim 1.

Claim 33 (original): A method of inhibiting oxidative stress-induced cell injury and/or death comprising:

providing a compound according to claim 1 and

contacting a cell with the compound, whereby the compound is taken up by the cell and enters mitochondria of the cell, thereby scavenging oxidative free radicals and/or reactive oxygen species to inhibit oxidative stress-induced cell injury and/or death.

Claim 34 (original): The method according to claim 33 wherein the cell is ex vivo.

Claim 35 (original): The method according to claim 33 wherein the cell is *in vivo*.

Claim 36 (original): The method according to claim 33 wherein the compound is selected from the group consisting of:

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L-y-glutamyl-L-cysteinylglycine choline ester;

D-γ-glutamyl-L-cysteinylglycine choline ester;

L-cysteine choline ester;

L-γ-glutamyl-L-cysteine choline ester;

D-γ-glutamyl-L-cysteine choline ester;

N-acetyl-L-cysteine choline ester;

D-2-(trimethylamino)ethyl-2,2-dimethylthiazolidine-4-carboxylic acid; and

L-2-(trimethylamino)ethyl-2,2-dimethylthiazolidine-4-carboxylic acid.

Claim 37 (currently amended): The method according to claim 33 wherein the compound is in the form of a pharmaceutical composition in admixture with a pharmaceutically acceptable carrier.

Claim 38 (original): The method according to claim 33 wherein the cell is a neuronal cell, muscle cell, liver cell, or kidney cell.

Claim 39 (original): A method of treating a condition associated with oxidative stress-induced cell injury and/or death comprising:

providing a compound according to claim 1 and

administering the compound to a patient having a condition associated with oxidative stress-induced cell injury and/or death, whereby the compound is taken up by cells at risk of oxidative stress-induced injury and/or death, and enters

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mitochondria of the cells to inhibit oxidative stress-induced injury and/or death thereof, thereby treating the condition.

Claim 40 (original): The method according to claim 39 wherein the condition associated with oxidative stress-induced cell injury and/or death is selected from the group consisting of stroke, neurodegenerative disease, trauma, muscular disorders, diabetes, ischemia-reperfusion tissue injury, hypoxic-induced tissue damage, migraines, congenital mitochondrial diseases, neuromuscular degenerative disorders, epilepsy, neuropathy, neurological and neuropsychological developmental delays, amyotrophic lateral sclerosis, renal tubular acidosis, and aging related diseases or disorders.

Claim 41 (original): The method according to claim 39 wherein said administering is carried out orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by implantation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, transdermally, transmucosally or via inhalation.

Claim 42 (original): The method according to claim 39 wherein said administering is repeated.

Claim 43 (original): The method according to claim 39 wherein the compound is selected from the group consisting of:

L-y-glutamyl-L-cysteinylglycine choline ester;

L-cysteine choline ester;

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L-y-glutamyl-L-cysteine choline ester;

D-y-glutamyl-L-cysteine choline ester;

N-acetyl-L-cysteine choline ester;

D-2-(trimethylamino)ethyl-2,2-dimethylthiazolidine-4-carboxylic acid; and

L-2-(trimethylamino)ethyl-2,2-dimethylthiazolidine-4-carboxylic acid.

Claim 44 (currently amended): The method according to claim 39 wherein the compound is in the form of a pharmaceutical composition in admixture with a pharmaceutically acceptable carrier.

Claim 45 (original): The method according to claim 39 wherein the cell is a neuronal cell, muscle cell, liver cell, or kidney cell.

Claims 46-54 (canceled).

Claim 55 (new): A method of making a compound of claim 1 comprising:

deprotecting an intermediate according to formula (III) or formula (IV)

$$R' \longrightarrow O \longrightarrow Z \longrightarrow N^{+} \longrightarrow Q^{2}$$

$$Q^{1}$$

$$Q^{1}$$

$$Q^{2}$$

$$Q^{2}$$

$$Q^{2}$$

$$Q^{2}$$

$$Q^{3}$$

$$Q^{2}$$

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wherein R' is a derivative of R having one or more protecting groups and said step of deprotecting removes the one or more protecting groups from R; and

exposing the deprotected intermediate to a cation scavenger agent to form the compound of formula (I) or formula (II), respectively.

Claim 56 (new): The method of claim 55, wherein the intermediate is deprotected with trifluoroacetic acid in dichloromethane, hydrogen bromide or hydrogen chloride in acetic acid, or tri-n-butyl phosphine.

Claim 57 (new): The method of claim 55, wherein the cation scavenger agent is triethyl silane.